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- (71) Applicant (*for all designated States except US*): CLINI-
CAL MICROARRAYS, INC. [US/US]; 6 Huron Drive,
Natick, MA 01760 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): MONTAGU, Jean,
I. [US/US]; 76 Walnut Place, Brookline, MA 02445 (US).
WEBB, Robert, H. [US/US]; Old Concord Road, Lincoln,
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
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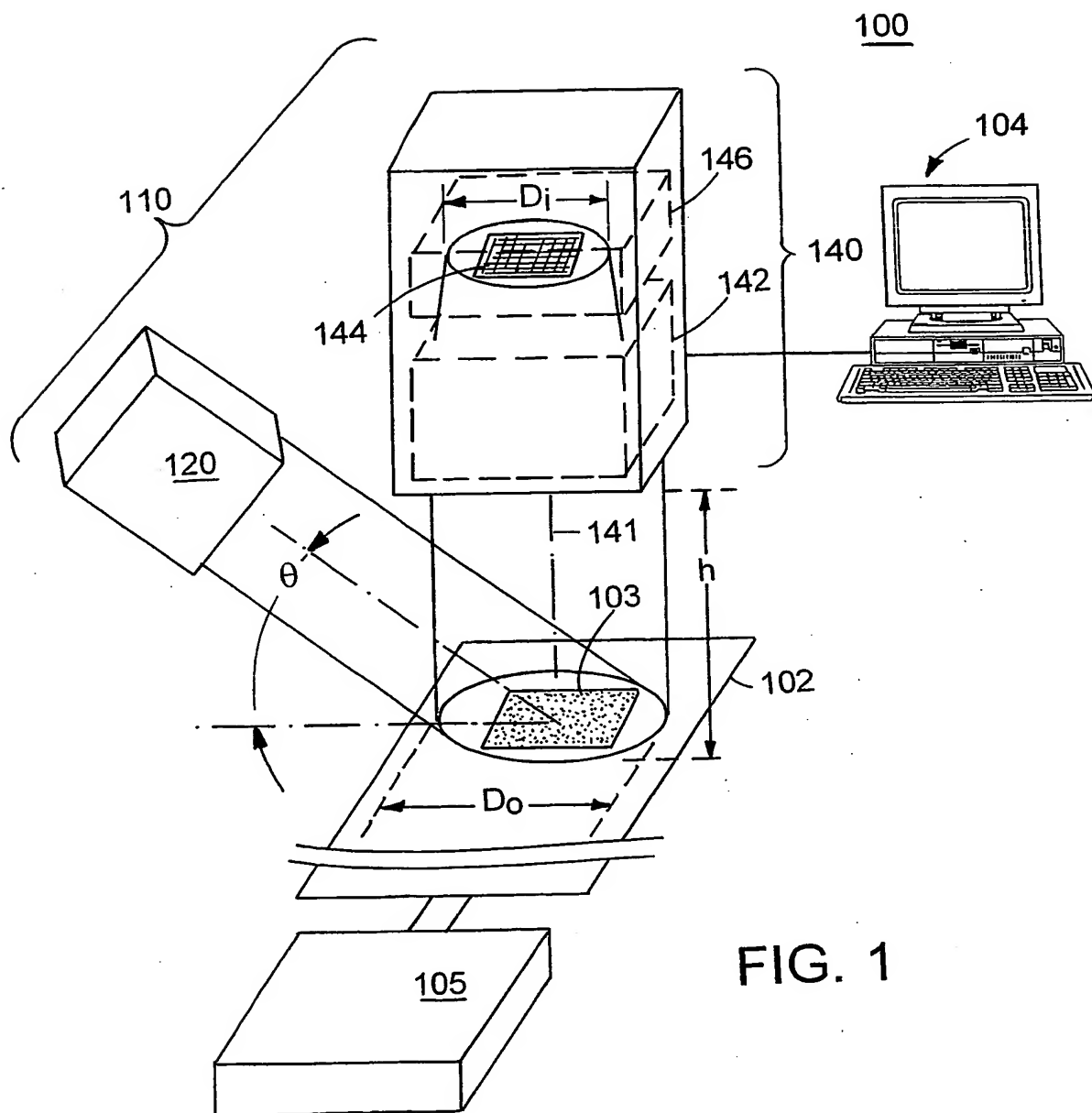
For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: READING OF FLUORESCENT ARRAYS

(57) Abstract: Reading of fluorescent arrays (103) in clinical settings is made possible by a reader (110) constructed to employ dark field illumination of the array, and mapping an image of the array onto a solid state sensor array (146) with image dimensions (D_i) of the same order magnitude as the dimensions (D_a) of the fluorescent array, preferably with reduction of image. High intensity illumination is employed, non uniformities of which being compensated by normalization employing intensity calibration features (164) in the array itself, that are sensed during imaging of the array. Preferably high intensity light emitting diodes (122, 132, 402, 404), such as used in traffic lights, are employed for excitation of the array, preferably the excitation being introduced to the array via a solid internally reflecting homogenizer (130). Intermediate depth of field collection and imaging optics enable substantial collection of light, with NA in the range of 0.30 to 0.60, preferably in the range of 0.4 to 0.55. The resultant relatively large depth of field is in some advantageous cases compensated by absorbing light that tends to travel beyond the spots being imaged and would otherwise create noise fluorescence, the absorption produced e.g., by an opaque metal oxide coating (304) that is interposed between a substrate (302), preferably an ultra-thin substrate, on which the array lies, and the much thicker glass or other rigid support (306). For clinical purposes the arrays comprise fewer than 1000 spots, as is appropriate for protein, one example being an array of fewer than 500 spots. Relatively large spot sizes are employed, i.e. of the order of at least 80 or 100 micron diameter spots or preferably larger, 150 or 300 micron spots. Resolution of such spots to at least 50 pixels on the solid state detector array enables suitable binning and other manipulations leading to highly accurate results. Novel methods of assays and diagnosis such as cancer diagnosis employ the reader in detecting a set of markers related to the disease, for instance ovarian cancer.

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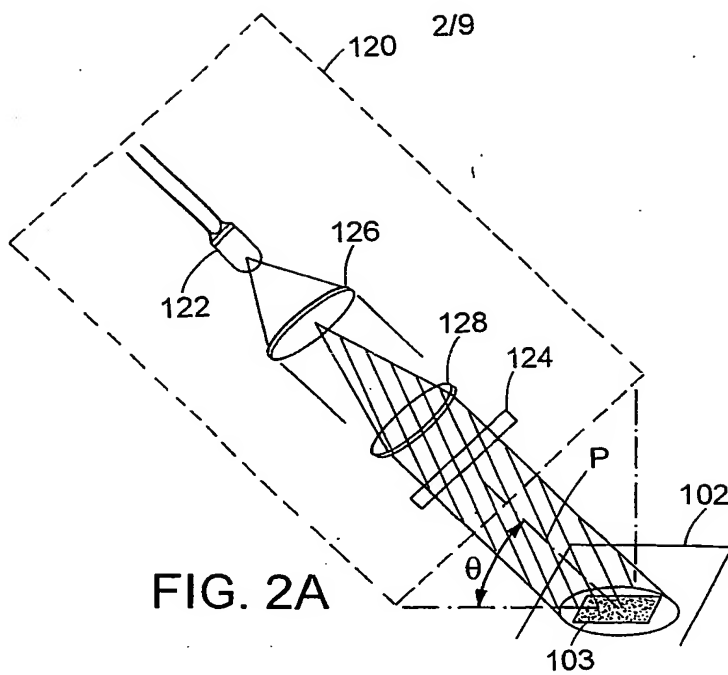


FIG. 2A

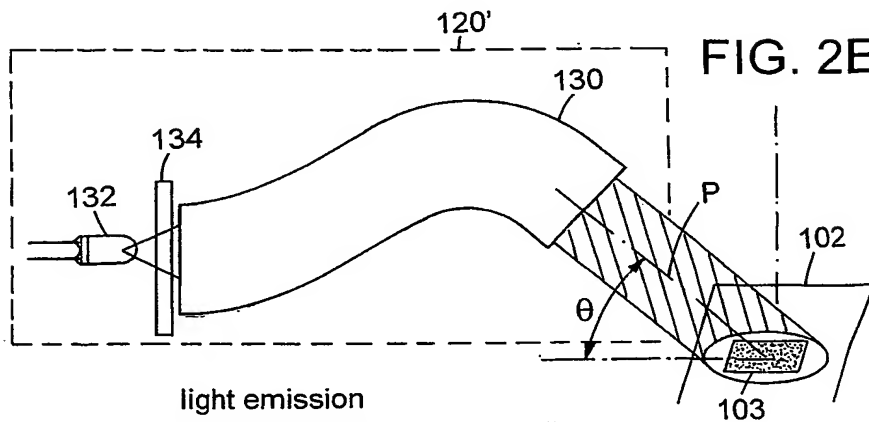


FIG. 2B

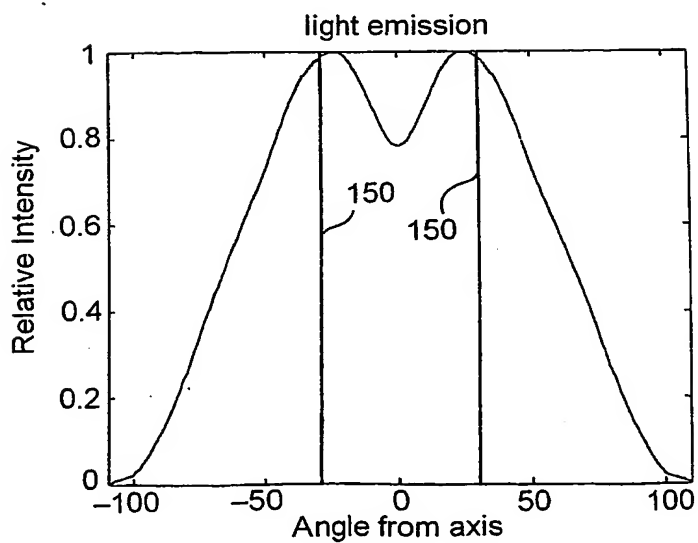


FIG. 3

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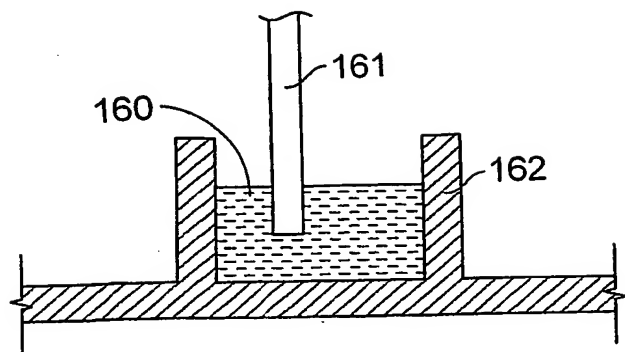


FIG. 4A

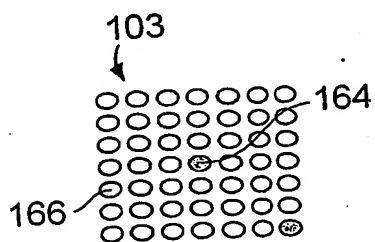


FIG. 4B

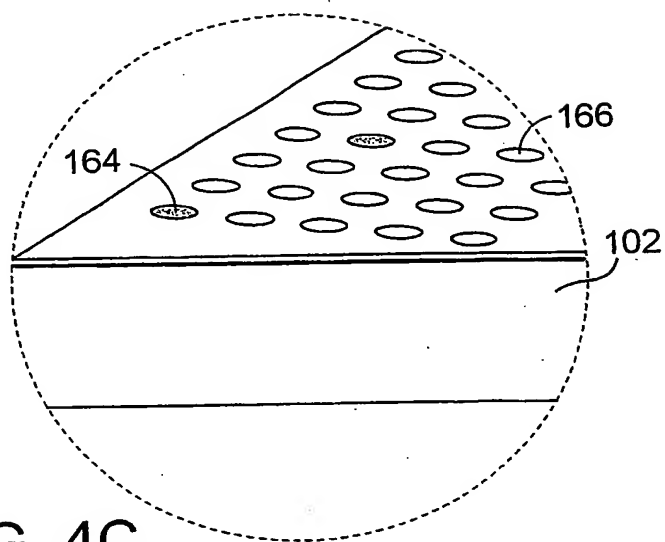


FIG. 4C

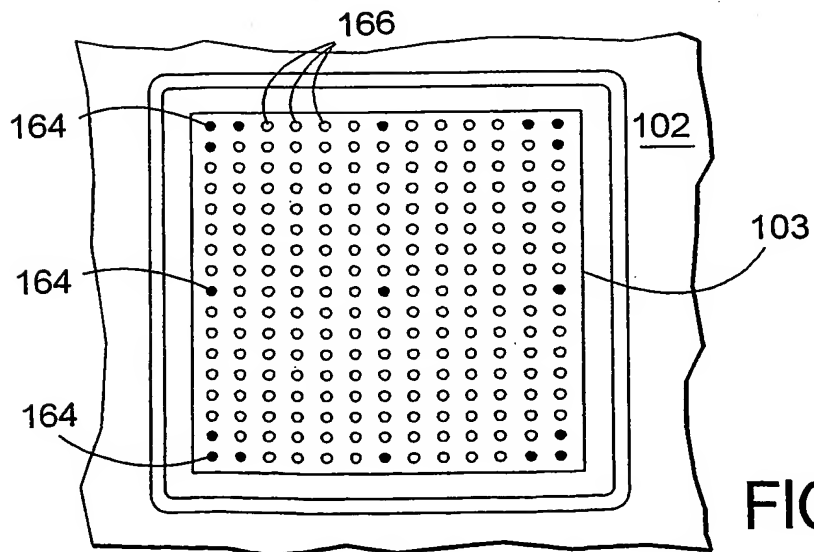


FIG. 4D

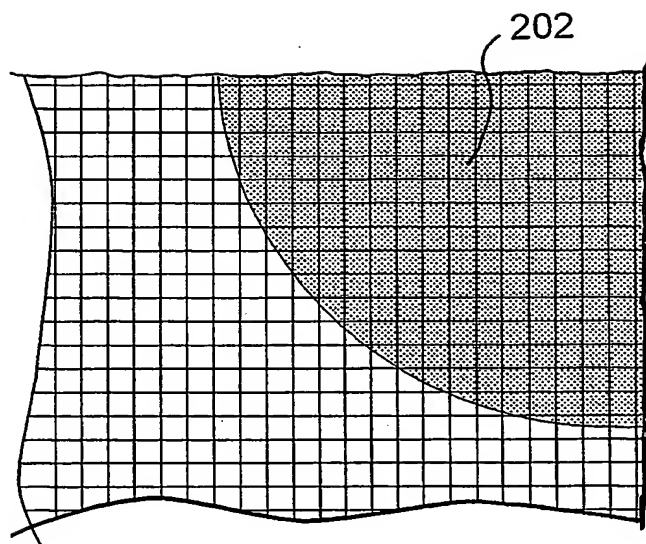


FIG. 5

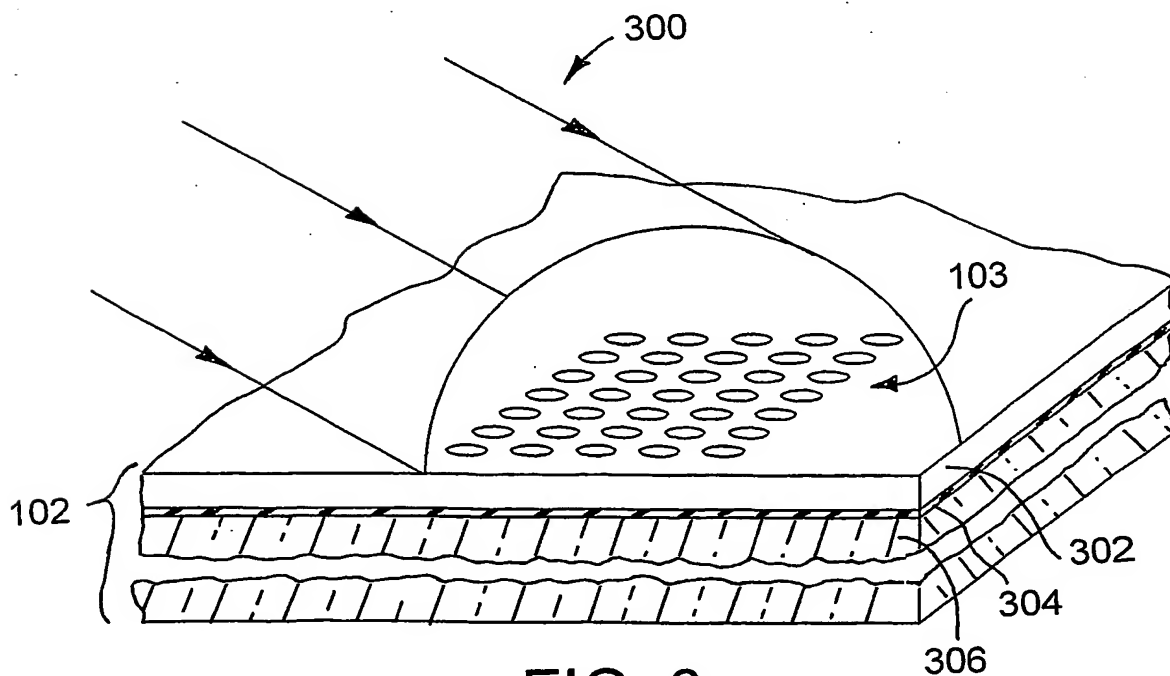


FIG. 6

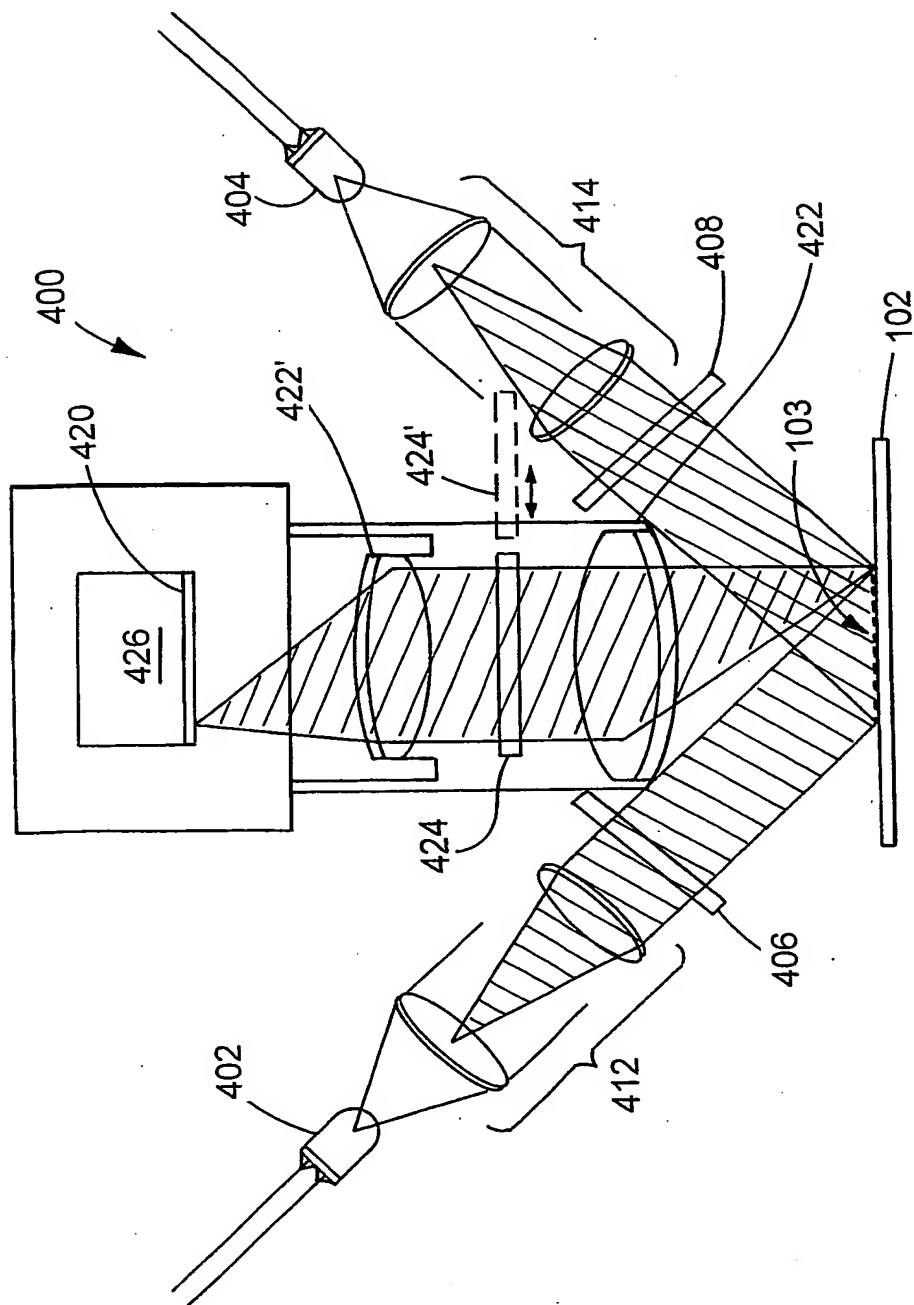


FIG. 7A

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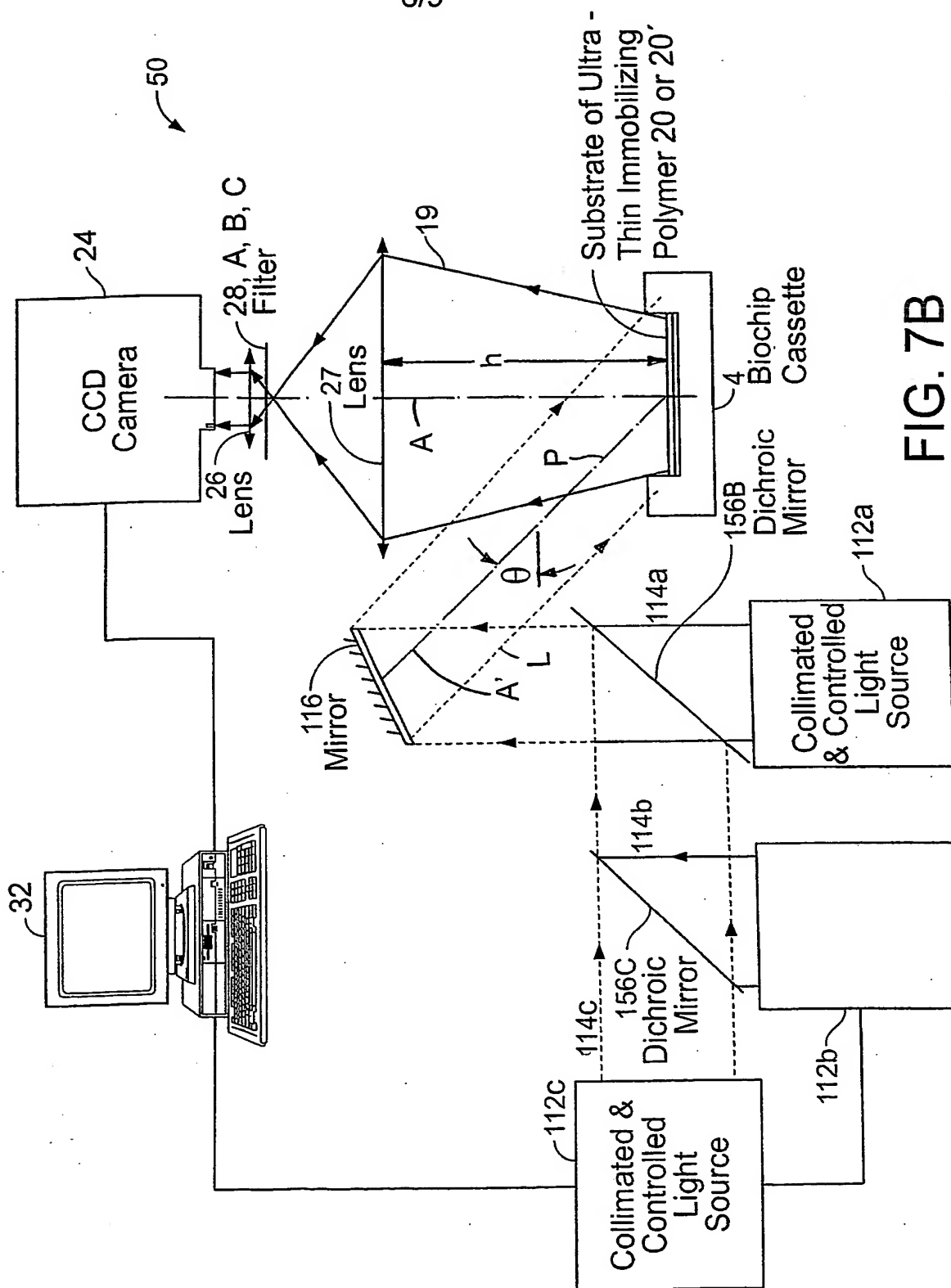


FIG. 7B

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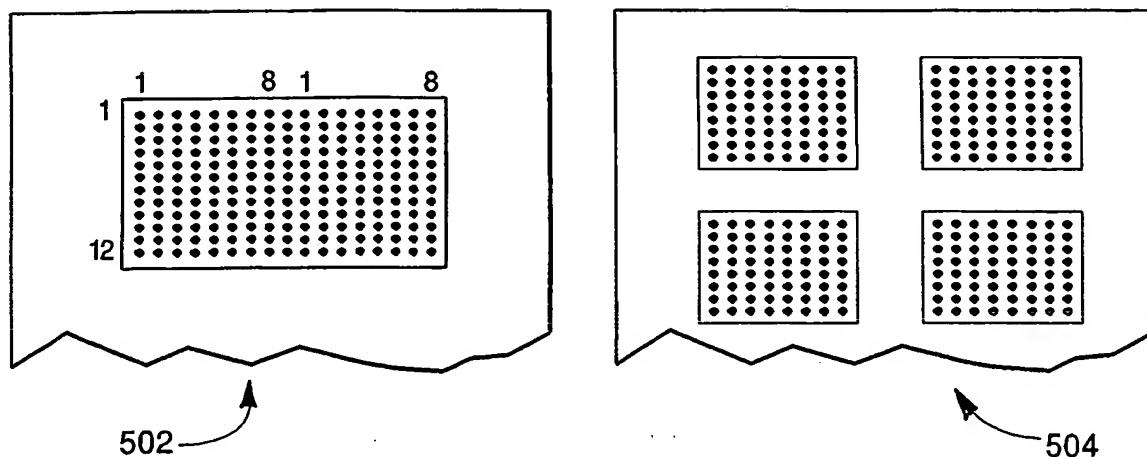


FIG. 8

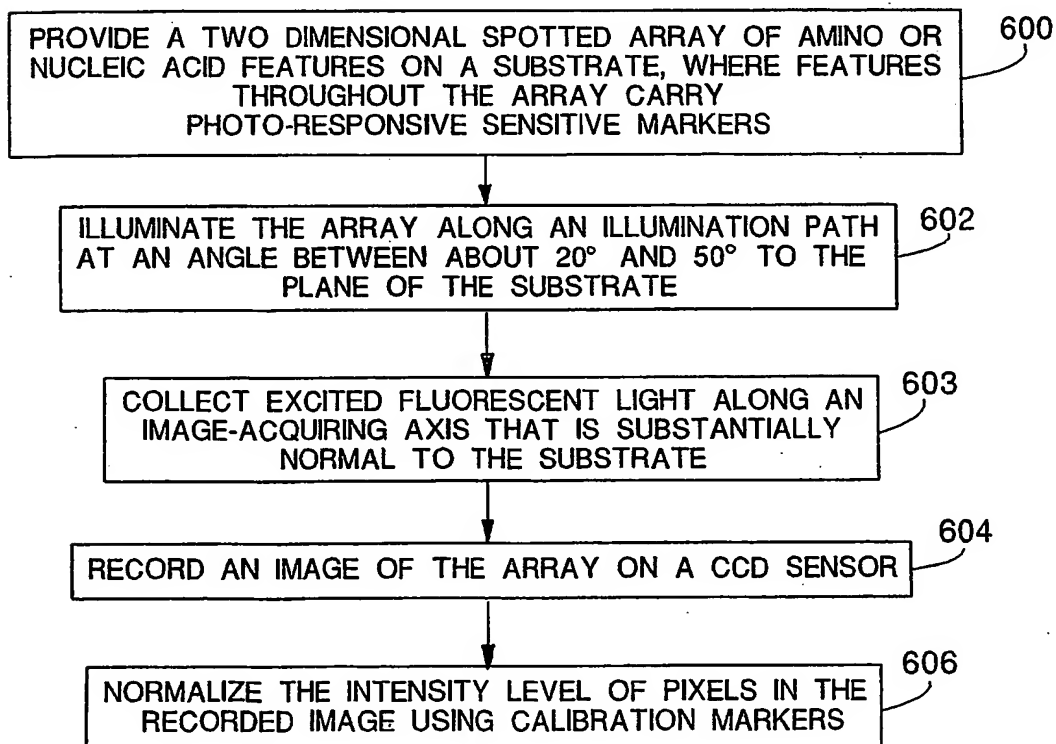


FIG. 9

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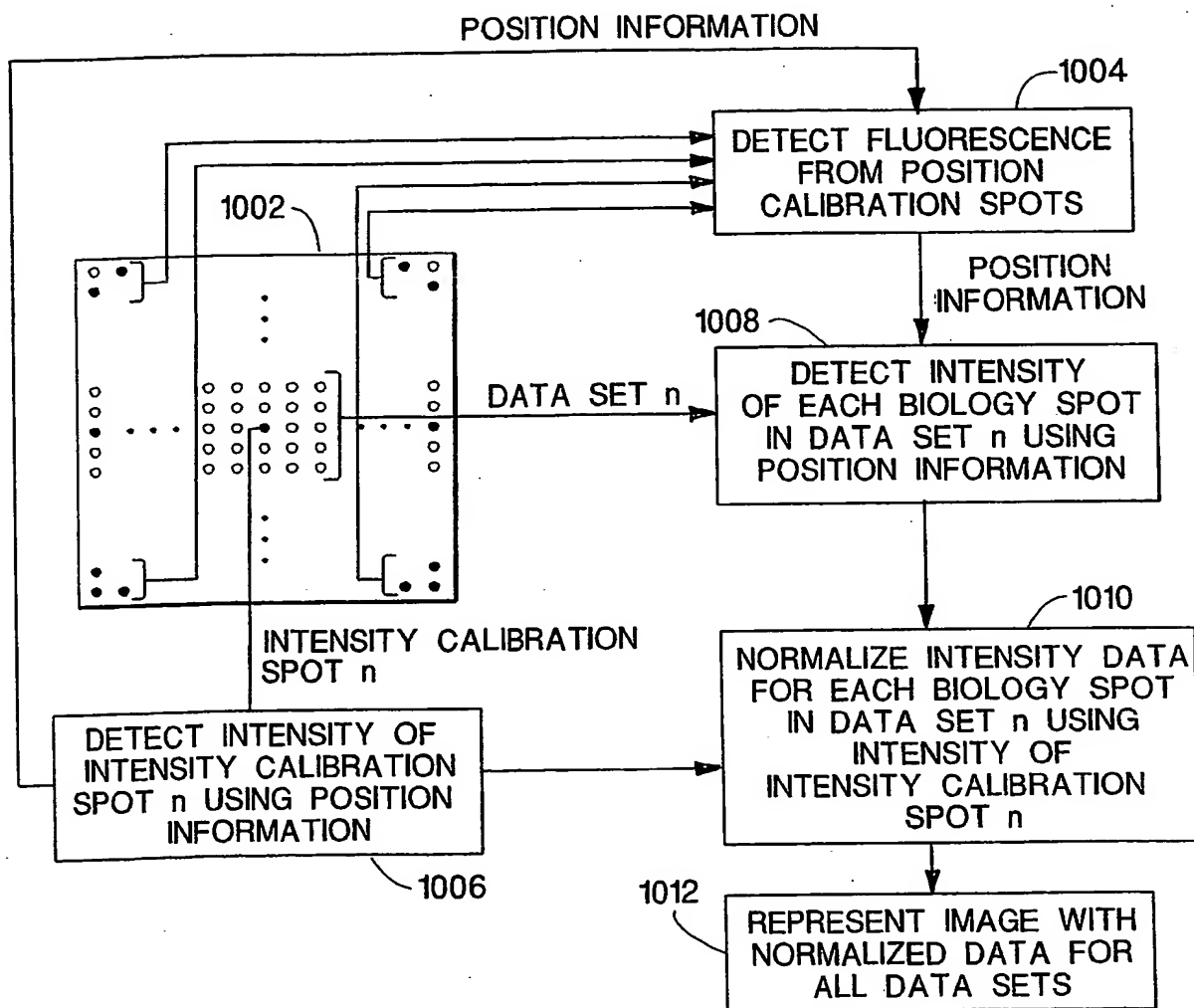


FIG. 10

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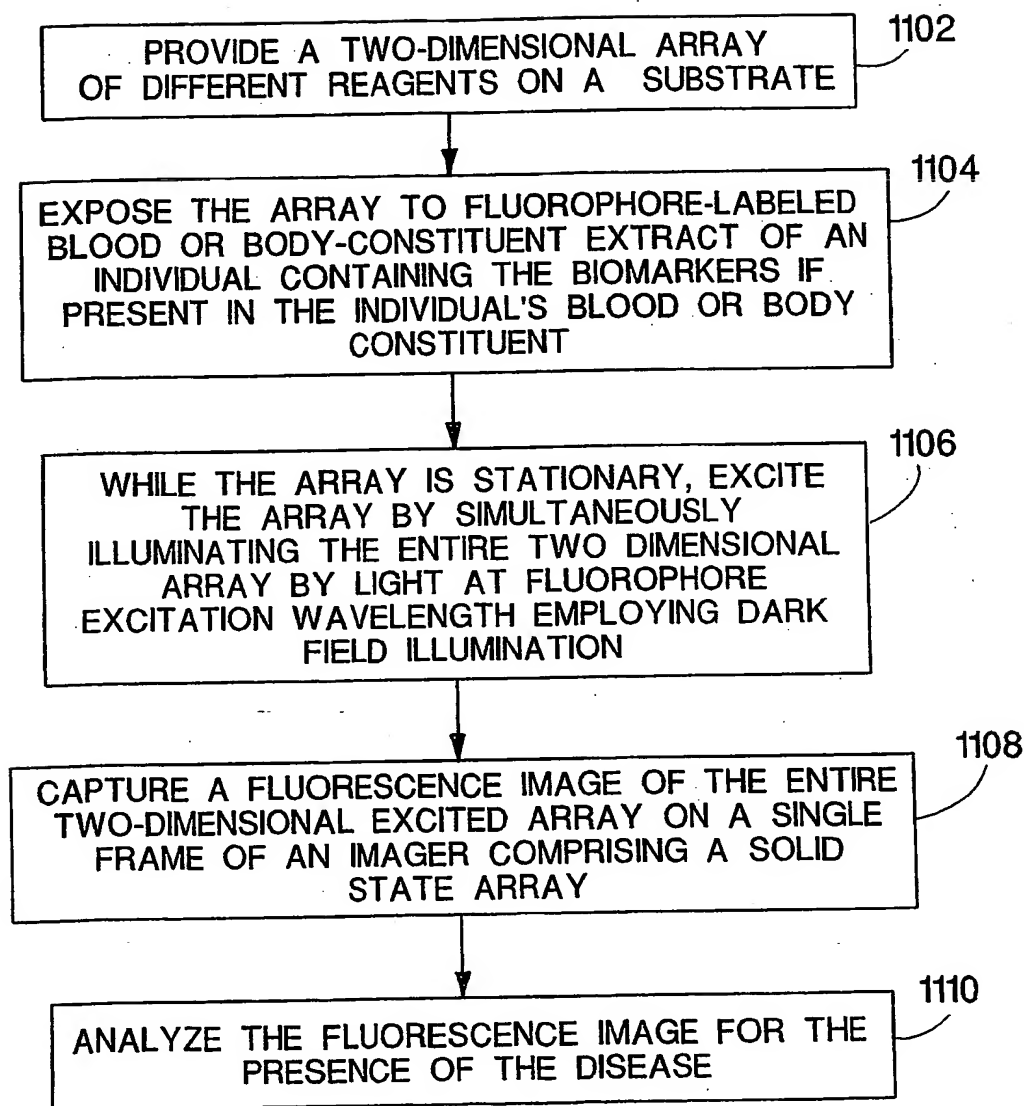


FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/25702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/543

US CL : 436/518

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 436/518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,294,136 B1 (SCHWARTZ) 25 September 2001 (25.11.2001), see entire document.	1, 17 ----- 2, 3, 45, 46
X --- Y	US 6,294,327 B1 (WALTON et al) 25 September 2001 (25.11.2001), see entire document.	1-2, 17, 45-47, 49 ----- 3, 39-41, 50
Y	US 6,007,996 A (MCNAMARA et al) 28 December 1999 (28.12.1999), see entire document.	1-3, 17, 39, 45, 46, 49, 50
Y, E	US 6,573,051 B2 (ALSMADI et al) 03 June 2003 (03.06.2003), see entire document.	45, 46, 49, 50

☐ Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z"

document member of the same patent family

Date of the actual completion of the international search

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Authorized officer

Nelson Yang

Telephone No. (703) 308-0196

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-31, drawn to an array reader.

Group 2, claim(s) 39-50, drawn to a fluorescence reader-based diagnostic method.

The inventions listed as Groups 1-2 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The application contains claims to more than one of the combinations of categories of inventions as set forth by 37 CFR 1.475.

According to 37 CFR 1.475 regarding unity of invention:

(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product; or
- (2) A product and a process of use of said product; or
- (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
- (4) A process and an apparatus or means specifically designed for carrying out the said process; or
- (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) above, unity of invention might not be present. Furthermore, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. The determination is made based on the contents of the claims as interpreted in light of the description and drawings. In the instant application, Groups 1-2 have differing special technical features:

Group 1 has the special technical feature of an array reader.

Group 2 has the special technical feature reading an array using an array reader.

Furthermore, the special technical feature of the apparatus of group 1 is known in the art as shown by Schwartz [US 6,294,136] for image processing and determining the size of individual nucleic acid molecules. Therefore the inventions do not form a general inventive concept, as they do not share a common special technical feature.